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Genetic and Environmental Effects on Myopia : The Healthy Twin Study

한국인의 근시와 관련된 유전 및 환경요인 분석

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서울대학교 보건대학원

보건학과 역학전공

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Abstract

Background: Despite of the recent increasing prevalence of myopia in Asia, the investigation of genetic and environmental factors for myopia in Asian populations has been limited.

Aim: The aim of this study was to identify environmental and genetic influences on myopia in the Healthy Twin Study comprised of twins and their family members.

Methods: Among the Healthy Twin Study, a total of 240 monozygotic twin pairs, and 45 dizygotic twin pairs, and 938 singleton adult family members who were first degree relatives of twins in 345 families were included in the study. Spherical equivalent, axial length, anterior chamber depth, and corneal astigmatism were measured by refraction, corneal topography, and A- scan ultrasonography. To estimate the effect of education and income on ocular traits, multiple linear regression analyses were performed including variables - such as age, sex, education groups, income groups and height. To assess the effect of education and income on the risk of myopia defined as ≤ -0.75 diopters, multiple logistic regression was used. Both linear and logistic regressions were done with the mixed model. To see the degree of resemblance among the different types of family relationships, intraclass correlation coefficients (ICC) were calculated with the mixed model. Variance-component methods were applied to estimate the genetic contributions to eye phenotypes.

Results: After adjusting for covariates, education was associated with a lower spherical equivalent of 0.21 diopters (P=0.01) and a longer anterior chamber depth by 0.03 mm (P=0.05), and income was associated with a lower spherical equivalent of 0.18 diopters (P=0.04), a longer axial length by 0.19 mm (P=0.0007) and a longer anterior chamber depth by 0.04 mm (P=0.01). Education level was associated with the risk of myopia (OR=1.84, 95% CI: 1.12-3.01). The ICCs of spherical equivalent and ocular biometrics were significantly higher in monozygotic twins compared to other relative pairs, with greater consistency and conformity. The estimated narrow sense heritability (95% CI) was 0.67 (0.59-0.76) for spherical equivalent, 0.78 (0.69-0.87) for axial length, 0.77 (0.69-0.84) for anterior chamber depth, and 0.18 (0.02-0.34) for corneal astigmatism.

Conclusion: Educational level was significantly associated with the risk of myopia. The compelling evidence for the estimated heritability of spherical equivalent and ocular biometrics in the Korean population suggests that all traits are highly heritable. Given the high heritability of myopia, the recent myopia epidemic in East Asia might be due to gene-by-environment interactions. Further studies are required to identify genetic factors and to examine gene-environment interactions, and then personalized prevention and treatment should be implemented in the future.

Keyword: Myopia, Refractive error, Heritability, the Healthy Twin Study
Student ID: 2012-21887

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List of Abbreviations

MZ: Monozygotic twins

DZ: Dizygotic twins

SE: Spherical equivalent

AL: Axial length

ACD: Anterior chamber depth

CA: Corneal astigmatism

D: Diopter

ICC: Intraclass correlation coefficient

SB: Sibling

I. INTRODUCTION

1. Background

Myopia, a form of refractive error, occurs when parallel light rays from distant objects come to focus in front of the retina.[1] Refractive error is quantified as spherical equivalent in a continual dioptric scale using the equation below.

$$\text{Spherical equivalent} = \text{Spherical error} + \frac{\text{Cylindrical error}}{2}$$

Spherical equivalent means the optical power of a lens necessary to correct the optical defect of the myopic or hyperopic eye.[2] Myopia is defined as a spherical equivalent ≤ -0.5 Diopters (D) or ≤ -0.75 D.[3] The refractive status of the eye is associated with the morphology of the eye and determined by the coordinated contributions of ocular biometrics, such as axial length, anterior chamber depth and corneal astigmatism.[1] It has been documented that a lower spherical equivalent, longer axial length, longer anterior chamber depth and higher cornea astigmatism are considered to be more myopic refraction.[4]

Axial length, the distance from the anterior cornea to the retinal pigment epithelium, has been suggested to be the major endophenotype of refractive error. Because the growth of the eye globe is related to physical development, height has been reported to be associated with axial length.[5, 6] While axial length is associated with refraction, the association of height with spherical equivalent is inconsistent.[5] Because refractive error is a complex phenotype highly correlated with other biometric parameters, it is important to investigate ocular biometrics as well as spherical equivalent to understand the development and risk factors of myopia.

Myopia is the most common ocular disorder worldwide. The prevalence of myopia is increasing all over the world, particularly in East Asian nations.[7-10] The expansion of mass intensive education in East Asia could be a reason for this increase.[8, 11] While both Asian and Western adult populations are similar in the prevalence of myopia ranging from 16.4% to 38.7% [7, 12], the prevalence of myopia in children and young adults has been reported to be higher in Asian populations such as Singapore and Taiwan ranging up to 80% compared to Western populations up to 30%.[13-16] There have been several studies on the prevalence of myopia in Korean populations. The Korea National Health and Nutrition Examination Survey 2008 -2009 revealed that there was a 54% prevalence of myopia defined as a SE $\leq$ -0.75 D in the population over 5 years of age.[3] The Namil Study reported the prevalence to be 20.5% for myopia with a SE $\leq$ -0.5 D in a rural Korean adult population that was over 40 years of age.[17] In a younger population, Lim et al. reported the prevalence to be 22.6% for myopia with a SE $\leq$ -0.75 D in children that were up to 18 years of age, and Lee et al. reported the prevalence to be 83.3 % for myopia with a SE $\leq$ -0.5 D in males that were 19 years of age.[18, 19]

With its increasing prevalence in recent birth cohorts, myopia is a significant global public health concern leading to ocular complication and legal blindness.[4] Myopia is a risk factor for several visual impairments such as retinal detachment, cataracts, glaucoma, macular choroidal neovascularization and macular degeneration.[1, 20-22] Myopia could also impede vision-related quality of life or tasks, resulting in economic burden.[4, 23]

Myopia is a complex multifactorial trait that is influenced by both environmental and genetic factors and, possibly, their interaction.[2, 24] Environmental risk factors of myopia have been well documented. Near work, such as reading or writing, has been considered to be a strong risk factor of myopia, and education, income and occupation have been reported to be a surrogate of near work.[2, 25, 26] A myriad of studies have identified associations of myopia with higher education levels, higher income levels and near work related occupations.[12, 25, 27-29] On the one hand, outdoor activity has shown a protective effect against the onset and progression of myopia.[30-32]

Although environmental factors have a great impact on myopia, it should be noted that genetic factors play an important role in the development of myopia. Twin studies have highlighted a higher concordance of refractive error between monozygotic (MZ) twins than between dizygotic (DZ) twins and showed that spherical equivalent is highly heritable with a heritability estimate ranging from 70% to 90%.[33-36] Other ocular biometrics have also been shown to be highly heritable; the heritability estimate of AL, ACD and CA ranges from 67% to 94%, 51% to 94% and 46% to 60%, respectively.[33-37] The results of twin studies indicate that genetic factors are involved in myopia.

However, despite the increasing prevalence of myopia in Asia, the investigation of genetic and environmental influences on myopia in Asian populations is still limited. In the Korean population, although several studies have investigated the prevalence and environmental risk factors of myopia, there is a lack of studies examining the genetic contribution to myopia.

2. Aims

The aim of this study was to identify the environmental and genetic influences on myopia in the Healthy Twin Study comprised of twins and their family members.

The detailed aims are listed below.

1) To estimate the environmental effects of education and income as a crude marker of near work on refractive error and ocular biometrics including axial length, anterior chamber depth and corneal astigmatism
2) To estimate the environmental effects of education and income on the risk of myopia measured by spherical equivalent
3) To identify the extent of the genetic contribution on refractive error and ocular biometrics including axial length, anterior chamber depth and corneal astigmatism by estimating heritability and intraclass correlation

II. METHODS

1. Study population

Participants are part of the Healthy Twin Study, a prospective cohort study that has recruited Korean adult twins and their family members based on a nation-wide registry through mailing and advertisements at public health agencies since 2005. Extensive eye exams were introduced in 2007 for newly recruited participants and for the follow-up visits of previously recruited participants in Seoul; in total, 1,688 individuals (665 men and 1023 women) underwent detailed eye examinations in the Department of Ophthalmology at the Samsung Medical Center in Seoul, Korea between the 2007 and 2011. A more detailed description of the recruitment and protocols of the study is available elsewhere.[38, 39] Among the total, 180 participants were excluded in that they had ocular disorders such as strabismus, keratoconus, glaucoma, cataracts, retinopathy or amblyopia, or had undergone prior eye surgery**.** The final sample size was 1,508 participants: 240 MZ twin pairs, 45 DZ twin pairs, and 938 singleton adult family members who were first degree relatives of twins in 347 families; 48 orphan MZ cotwins and 12 orphan DZ cotwins were regarded as singletons, and spouses of twins were included only when their adult offspring participated as well. The sample included 1,361 parent-offspring pairs (235 father-son pairs, 304 father-daughter pairs, 349 mother-son pairs, and 473 mother-daughter pairs), and 1,407 sibling pairs (603 sister pairs, 303 brother pairs, and 501 sister-brother pairs) and 214 spouse pairs. For each trait, different numbers of participants were available: 1,504 individuals for spherical equivalent, 982 individuals for axial length and 1,333 individuals for anterior chamber depth and corneal astigmatism. All participants provided written informed consent. The study protocol was approved by the institutional review board of the Samsung Medical Center. The zygosities of participating twin pairs were identified by 16 short tandem repeat (STR) markers (15 autosomal markers and one sex-determining marker) in 67% of the twin pairs. For the remaining 33%, zygosity was determined based on a self-administered zygosity questionnaire, of which the positive predictive value was 97.2% for MZ and 95.0% for DZ.[40]

2. Measurements

Participants underwent non-dilated refraction measurements with an autorefractor (Topcon AT, Tokyo, Japan). A total of 3 readings were taken in each eye, and the average value for each eye was recorded. Refractive error was calculated as the mean spherical equivalent (SE) for each eye measured in diopters using the standard formula mentioned above. Axial length (AL) was measured by corneal touch A-scan ultrasonography (Model 820; Allergan-Humphrey, San Leandro, CA, USA). Computed corneal topographic analysis (Orbscan, Bausch and Lomb, Buffalo, NY, USA) was performed to obtain anterior chamber depth (ACD) and keratometry. Corneal astigmatism (CA) was obtained by using a simulated keratometry value from the corneal topography.

3. Definitions of education and income

Education and income level were grouped into three categories each for the analysis. Education was categorized into less than 10 years, 10 to 12 years and more than 12 years. Monthly income was categorized into less than 1.5 million Korean won (KRW), 1.5 to 3.0 million KRW and more than 3.0 million KRW (approximate exchange rate 1,200 won = US$1).

4. Statistical Analysis

All analyses were carried out using the average of both eyes for each parameter, because the correlation between two eyes for SE and ocular biometrics was high. Four outcome variables, SE, AL, ACD and CA, were analyzed as continuous variables. Myopia was defined as a SE $\leq$ -0.75D. t-test and analysis of variance (ANOVA) were performed to evaluate the significant difference of mean trait between males and females and among the age, education and income groups, respectively.

To estimate the effect of education and income on SE and ocular biometrics, multiple linear regression analyses were performed which included variables, such as age, sex, education groups, income groups and height. To assess the effect of education and income on the risk of myopia, multiple logistic regression was used. Both linear and logistic regressions were conducted with the mixed model in which household effects were included as random effects to adjust for familial aggregation.

To determine the degree of resemblance among different types of family relationships, intraclass correlation coefficients (ICC) were calculated after adjusting for age and sex for non-twins. ICCs are estimated by the specific family type or as pooled estimates among those with the same genetic distance; e.g., pooled ICC of DZ and sibling pairs both of which are all first degree relatives that share 50% of genetic information on average. After testing for normality, a mixed model was used to calculate ICCs where the ICC is calculated as a proportion of covariance within a particular family relationship over total variance, a sum of within group variance and residual variance. Descriptive statistics and ICC calculations were performed using SAS (version 9.3; SAS Inc, Cary, NC, USA).

Variance-component methods were applied to estimate the genetic contributions to eye phenotypes as heritability. This study used extended families as well as twins, which can exclude dominance genetic effects and consider all types of family relationship.[41] Narrow sense heritability is calculated as the proportion of the total phenotypic variance explained by additive genetic effects. Linear and non-linear effects of age, sex, and interactions between age and sex were adjusted, such as age, sex, age^2, age-by-sex interaction, and age^2-by-sex interaction. After testing the genetic models including additive genetic effects, unmeasured shared environments, and unique environments, the best-fitting model is determined based on the maximum likelihood estimation. Heritability was estimated using a variance-components model implemented in the Seuquential Oligogenic Linkage Analysis Routines software package (version 4.0.7; http://solar.sfbrgenetics.org/).

III. RESULTS

1. Basic Description

Figure 1 shows the distribution of SE and the three ocular biometric components of the average of both eyes. The distribution of SE and AL was slightly skewed, but ACD was normally distributed. Because CA was skewed to the right, natural log transformation was used (Figure 2). Based on the cutoff points of myopia (SE ≤ -0.75D), the proportion of myopia was 47.07%.

Table 1 shows the basic characteristics of the refractive phenotypes of the study participants by age groups and sex. There were significant differences of in the mean traits between the males and females. In general, the females had lower SE, shorter AL, shorter ACD and higher CA compared to the males within all age groups. For SE, in the 40 - 49-year-old age group, the females had significantly lower values compared to the males ($P=0.01$). For AL, the females had a shorter axial length compared to the males with significance in all of the age groups ($P<0.01$). For ACD, the females had a shorter anterior chamber depth compared to the males with significance in the 30 – 39-year-old age group and in the over 50-year-old age group ($P<0.01$). For CA, the females had a significantly higher value compared to the males in the 40 – 49-year-old age group and in the over 60-year-old age group ($P<0.05$). Within each mean trait by sex, there were significant differences for all traits by age groups (data not shown) ($P<0.0001$). Among education and income groups, there were significant differences in mean traits, but the means of CA by income groups were not statistically different (P=0.17). Between males and females, the mean traits by education and income groups were not significantly different (data not shown). In general, each education and income groups showed a consistent trend in which higher education groups and higher income groups had a lower SE, longer AL, longer ACD and higher CA. For all traits, the males were significantly taller than the females.

Figure 1. Distribution of spherical equivalent and ocular biometrics

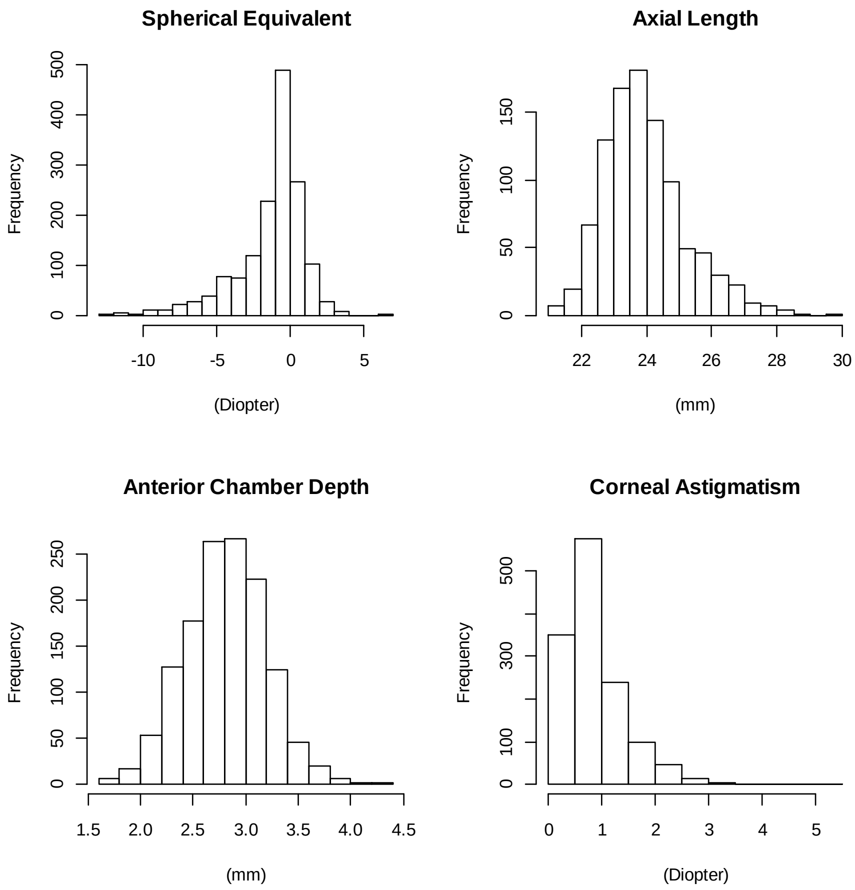

Figure 2. Distribution of transformed corneal astigmatism

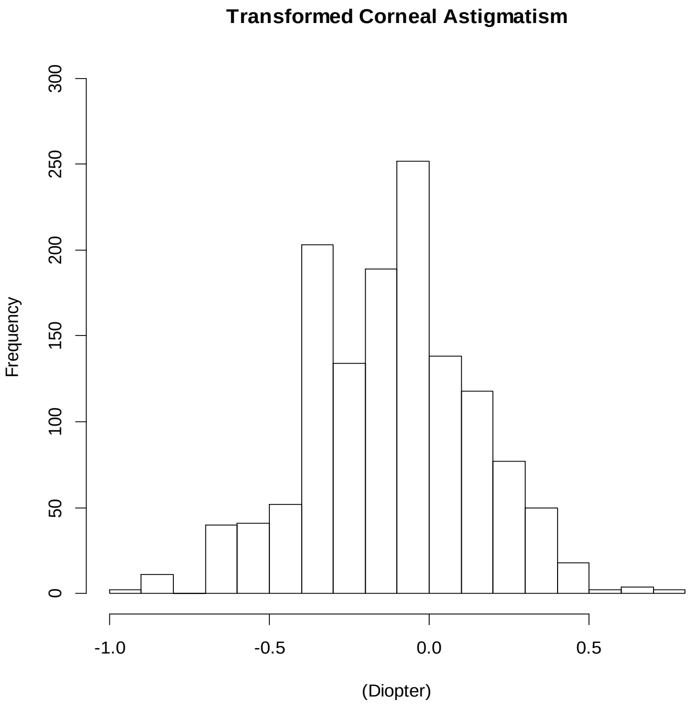

Table 1. Characteristic of refractive phenotypes of the study participants by age group and sex

	SE (D)			AL (mm)			ACD (mm)			CA (D)		
	Male (610)	**Female (894)**	**P value†**	**Male (386)**	**Female (596)**	**P value**	**Male (549)**	**Female (784)**	**P value**	**Male (549)**	**Female (784)**	**P value**
Age group, year												
~29	-2.49 ± 2.07	-3.13 ± 2.43	0.06	25.03 ± 1.27	24.41 ± 1.23	0.006	3.20 ± 0.33	3.14 ± 0.25	0.22	1.15 ± 0.69	1.35 ± 0.73	0.07
30~39	-1.79 ± 2.04	-1.99 ± 2.43	0.32	24.52 ± 1.11	24.03 ± 1.30	0.0004	3.03 ± 0.32	2.88 ± 0.35	<0.0001	0.97 ± 0.64	0.99 ± 0.63	0.70
40~49	-0.88 ± 1.51	-1.37 ± 2.10	0.01	24.14 ± 1.06	23.46 ± 1.32	0.0006	2.81 ± 0.29	2.74 ± 0.33	0.06	0.74 ± 0.45	0.85 ± 0.57	0.04
50~59	-0.16 ± 1.43	-0.42 ± 2.25	0.26	23.83 ± 0.97	23.38 ± 1.24	0.008	2.70 ± 0.30	2.52 ± 0.35	<0.0001	0.72 ± 0.43	0.80 ± 0.45	0.18
60~	0.54 ± 1.63	0.41 ± 1.55	0.57	23.66 ± 0.70	23.29 ± 0.91	0.01	2.63 ± 0.36	2.43 ± 0.36	0.0005	0.72 ± 0.37	0.90 ± 0.54	0.01
Total	-1.04 ± 2.03	-1.38 ± 2.44	0.003	24.26 ± 1.13	23.75 ± 1.30	<0.0001	2.89 ± 0.38	2.76 ± 0.40	<0.0001	0.86 ± 0.56	0.96 ± 0.61	0.004
Education, years	(607)	(892)		(383)	(595)		(546)	(782)		(546)	(782)	
< 9	0.17 ± 1.20	-0.07 ± 1.61		23.64 ± 0.82	23.27 ± 1.00		2.68 ± 0.33	2.55 ± 0.36		0.78 ± 0.42	0.85 ± 0.50	
10~12	-1.15 ± 2.10	-1.26 ± 2.33	<0.0001	24.36 ± 1.16	23.64 ± 1.34	<0.0001	2.89 ± 0.35	2.73 ± 0.38	<0.0001	0.86 ± 0.61	0.93 ± 0.54	0.005
> 12	-1.34 ± 2.08	-2.20 ± 2.58		24.39 ± 1.14	24.10 ± 1.31		2.95 ± 0.37	2.90 ± 0.36		0.89 ± 0.58	1.03 ± 0.70	
Income, won	(554)	(810)		(344)	(527)		(496)	(711)		(496)	(711)	
< 1.5 million	-0.77 ± 1.74	-1.22 ± 2.37		24.01 ± 0.93	23.64 ± 1.33		2.82 ± 0.33	2.71 ± 0.38		0.80 ± 0.53	0.93 ± 0.60	
1.5 million~3.0 million	-1.13 ± 2.34	-1.49 ± 2.23	<0.0001	24.32 ± 1.39	23.88 ± 1.09	<0.0001	2.89 ± 0.42	2.91 ± 0.38	<0.0001	0.86 ± 0.50	0.93 ± 0.59	0.17
≥3.0 million	-1.67 ± 2.33	-2.34 ± 2.83		24.69 ± 1.10	24.10 ± 1.46		3.04 ± 0.40	2.89 ± 0.43		0.96 ± 0.72	1.00 ± 0.60	
Height, cm	(610)	(894)		(386)	(596)		(549)	(784)		(549)	(784)	
	170.19±6.28	157.15±5.58	<0.0001	170.59±6.32	157.20±5.46	<0.0001	170.27±6.27	157.26±5.42	<0.0001	170.27±6.27	157.26±5.42	<0.0001

Mean ± S.D.; N in brackets

SE : Spherical Equivalent, AL : Axial Length, ACD : Anterior Chamber Depth, CA : Corneal Astigmatism, D : Diopter

†P value for age group and height: between male and female, P value for education and income: among groups

2. Regression analysis with environmental factors

Table 2 presents multiple linear regression coefficients for SE and ocular biometrics. After adjustment for age, sex, education, income and height if applicable, education was associated with SE and ACD, and income was associated with SE, AL and ACD. Height was strongly associated with AL and ACD, and slightly with CA, but was not related with SE. Refractions that tend to be toward myopia were more likely in individuals who were younger, and female, and included in the higher education and income group. For example, individuals with a higher education level had 0.21 diopters more myopic refraction, and individuals with a higher income level had 0.18 diopters more myopic refraction. A longer AL and ACD were associated with a younger age and a higher education and income level and height. For example, individuals with a higher income level had a longer AL by 0.19 mm, and individuals who were 1 centimeter taller had a longer AL by 0.05 mm. For ACD, individuals with a higher education and income level and who were 1 centimeter taller had a longer ACD 0.03 mm, 0.04 mm and 0.01 mm, respectively. CA was not significantly associated with education and income after adjusting for variables. Height was slightly associated with CA.

Table 3 shows the ORs of the multiple logistic regression analysis for the risk of myopia defined as a SE ≤ -0.75D. After adjusting for age, sex, education, income and height if applicable, the highest education group was associated with the risk of myopia (OR=1.84, 95% CI: 1.12-3.01). Other than the age groups, the ORs of the other covariates were not statistically significant.

Table 2. Coefficients of multiple linear regression analyses of spherical equivalent and ocular biometric parameters

	SE(D)				AL(mm)				ACD(mm)				CA(D)			
	Crude (S.E.)	**P value**	**Adjusted (S.E.) †**	**P value**	**Crude (S.E.)**	**P value**	**Adjusted (S.E.)**	**P value**	**Crude (S.E.)**	**P value**	**Adjusted (S.E.)**	**P value**	**Crude (S.E.)**	**P value**	**Adjusted (S.E.)**	**P value**
Age, years	0.08 (0.004)	<.0001	0.07 (0.01)	<.0001	-0.03 (0.002)	<.0001	-0.02 (0.003	<.0001	-0.02 (0.001)	<.0001	-0.01 (0.001	<.0001	-0.009 (0.001)	<.0001	-0.01 (0.002	<.0001
Sex, female	-0.33 (0.11)	0.004	-0.47 (0.18)	0.01	-0.50 (0.07)	<.0001	0.23 (0.13)	0.07	-0.14 (0.02)	<.0001	-0.04 (0.03)	0.18	0.10 (0.03)	0.002	0.02 (0.06)	0.72
Education, per category	-0.91 (0.07)	<.0001	-0.21 (0.08)	0.01	0.44 (0.05)	<.0001	0.07 (0.06)	0.22	0.18 (0.01)	<.0001	0.03 (0.01)	0.05	0.07 (0.02)	0.001	-0.01 (0.03)	0.78
Income, per category	-0.48 (0.10)	<.0001	-0.18 (0.09)	0.05	0.34 (0.06)	<.0001	0.17 (0.06)	0.002	0.11 (0.02)	<.0001	0.04 (0.01)	0.01	0.04 (0.03)	0.14	0.02 (0.03)	0.55
Height, cm	-0.02 (0.007)	0.001	-0.004 (0.01)	0.72	0.05 (0.04)	<.0001	0.05 (0.01)	<.0001	0.02 (0.001)	<.0001	0.01 (0.002)	0.0002	-0.003 (0.002)	0.15	-0.01 (0.003)	0.05

†Adjusted for age, sex, education, income, height

SE : Spherical Equivalent, AL : Axial Length, ACD : Anterior Chamber Depth, CA : Corneal Astigmatism, D : Diopter

Table 3. OR of logistic regression analyses of myopia

	Crude	(95% CI)	Adjusted†	(95% CI)
Age, years				
~29	1		1	
30~39	0.45	(0.27-0.72)	0.47	(0.27-0.81)
40~49	0.17	(0.11-0.28)	0.20	(0.11-0.35)
50~59	0.07	(0.04-0.12)	0.10	(0.05-0.19)
60~	0.03	(0.01-0.05)	0.04	(0.02-0.08)
Sex				
Male	1		1	
Female	1.14	(0.91-1.42)	1.30	(0.82-2.05)
Education, years				
< 10	1		1	
10~12	4.26	(2.96-6.14)	1.49	(0.93-2.39)
> 12	7.04	(4.93-10.05)	1.84	(1.12-3.02)
Income, won				
< 1.5 million	1		1	
1.5 million~ 3.0 million	1.16	(0.84-1.61)	0.84	(0.57-1.23)
> 3.0 million	2.55	(1.67-3.89)	1.57	(0.97-2.55)
Height, cm	1.03	(1.01-1.04)	1.00	(0.97-1.03)

†OR adjusted for age, sex, education, income and height

3. Intraclass correlation of spherical equivalent and ocular biometrics

The ICCs adjusted for age and sex where necessary are presented in Table 4. For SE, 239 MZ twin pairs, 45 DZ twin pairs, 352 sibling pairs, and 142 spouse pairs were included. For AL, 161 MZ twin pairs, 28 DZ twin pairs, 180 sibling pairs, and 100 spouse pairs were included. For ACD and CA, 206 MZ twin pairs, 35 DZ twin pairs, 331 sibling pairs, and 121 spouse pairs were included. For the pooled first degree pairs, pairs were added as cases of one sibling with DZ twins and a singleton of the DZ twins with siblings were included. The ICCs from the MZ twin pairs, pooled first degree pairs, and spouse pairs were 0.83, 0.34 and 0.20, respectively, for SE; 0.87, 0.40 and 0.24, respectively, for AL; 0.90, 0.49 and 0.09, respectively, for ACD; and 0.64, 0.20, 0.04, respectively, for CA.

Table 4. Intraclass correlation coefficient (95% CI) for spherical equivalent and ocular biometric parameters

Trait	**MZ**		**1st degree relatives**						**Spouse†**	
			DZ		**SB†**		**DZ+SB**			
	N	**ICC**	**N**	**ICC**	**N**	**ICC**	**N**	**ICC**	**N**	**ICC**
SE (D)	239	0.83	45	0.46	352	0.40	507	0.34	142	0.20
AL (mm)	161	0.87	28	0.56	180	0.47	261	0.40	100	0.24
ACD mm)	206	0.90	35	0.71	331	0.47	447	0.49	121	0.09
CA (D)	206	0.64	35	0.30	331	0.20	447	0.20	121	0.04

†Adjusted for age and sex; N (pairs)
SE : Spherical Equivalent, AL : Axial Length, ACD : Anterior Chamber Depth, CA : Corneal Astigmatism, D : Diopter
MZ : Monozygotic twin, DZ : Dizygotic twin, SB : Sibling
ICC : Intraclass Correlation Coefficient

4. Heritability of spherical equivalent and ocular biometrics

In this study, variance component algorithm-based heritability was determined based on the maximum likelihood. The best-fitting model was an ACE model for all ocular traits (Table 5). The estimated narrow sense heritability (95% CI) was 0.67 (0.59-0.76) for SE, 0.78 (0.69-0.87) for AL, 0.77 (0.69-0.84) for ACD, and 0.18 (0.02-0.34) for CA. For all traits, two types of shared environment components, household effects and sibling effects, were analyzed. The ACE model given the sibling effects as a shared environment component had the maximum likelihood in all traits.

Table 5. Variance components and heritability estimates for spherical equivalent and ocular biometrics parameters

Trait	**Variance component**			**Best-fitting model**	**Narrow sense heritability (h2 ± S.E.)**
	A	**C**	**E**		
SE(D)	0.67**	0.14*	0.19	ACE	0.67 ± 0.04
AL(mm)	0.78**	0.09*	0.13	ACE	0.78 ± 0.04
ACD(mm)	0.77**	0.15*	0.09	ACE	0.77 ± 0.04
CA(D)	0.18*	0.23*	0.59	ACE	0.18 ± 0.08

After adjusted for age, sex, age^2, age×sex, and age^2×sex
A: additive genetic effects, C: shared environment effects with siblings, E: unique environment effects, h2 : heritability
SE : Spherical Equivalent, AL : Axial Length, ACD : Anterior Chamber Depth, CA : Corneal Astigmatism, D : Diopter
*P<0.05, **P<0.0001

IV. DISCUSSION

The aim of this study was to evaluate the environmental and genetic contributions to refraction and ocular biometrics in the Healthy Twin Study. First, this study confirmed the association of education and income with myopia. In regards to continuous ocular traits, subjects with more myopic refraction had a higher education and income level based on the multiple linear regression analysis. In addition, when the trait was considered as a binary scale, higher education level was significantly associated with the risk of myopia based on the multiple logistic regression analysis. Second, this study revealed that the intraclass correlation coefficients for ocular traits were higher in MZ twins compared with other relative pairs, and SE and ocular biometrics were strongly heritable supporting previous evidence.

The present study can provide hints on the recent myopia epidemic in East Asia. Several studies have suggested that an increasing prevalence of myopia in Asian populations could be due to the concurrent increase in education concern in a younger generation as a strong environmental influence.[26, 42] However, considering the strong genetic influence on myopia, a rapid change would not be attributed to only an environmental change. It is more reasonable to argue that there are gene-environment interactions. It can be postulated that the growing educational concern in East Asia could have an influence on the myopia gene. Verhoeven et al. examined a robust gene-environment interaction and showed that education level and genetic risk of myopia interact with each other.[43] This study discussed that near work such as education would be essential to trigger myopia gene expression. The gene-environment interaction for myopia should be examined more thoroughly in future studies to elucidate the nature of the myopia epidemic worldwide and the biological mechanism of myopia.

Numerous studies have suggested that education, income and occupation can be a surrogate for near work which is the most noted risk factor for myopia. A higher level of education requires intensive near work such as reading or writing, and this could cause myopia progression. It has been proven that individuals with myopic eye have a significant association with educational level. [17, 18, 25] In the present study, the risk of myopia was strongly associated with the highest education level after adjusting for age, sex, income and height (OR=1.84, 95% CI: 1.12-3.01). However, income failed to show a significant relationship with the risk of myopia. The results suggest that although education and income have been suggested to be a surrogate of near work, each of them might have a different impact on myopia. Other ocular traits, such as axial length and anterior chamber depth, were associated with education and income. This result was consistent with previous studies; Wong et al. investigated the relation of education, occupation and socioeconomic status to ocular traits and showed that adults with more education and near work related occupations and higher income tend to have longer axial lengths and vitreous chambers.[25] Further investigations with more accurate risk factors or a compact index could provide more convincing evidence for the association of near work with myopia.

The present study considered not only refractive error but also its associated ocular components to investigate the environmental and genetic influences on myopia.

This study confirmed that axial length and anterior chamber depth were associated with education, income and height, and were highly heritable. Even though corneal astigmatism had no significant association with education, income and height, the trait showed a myopic trend that individuals with higher corneal astigmatism were in higher education and income groups. In addition, even though the heritability of corneal astigmatism was low, the statistical significance was substantial ($P<0.0001$). Especially, axial length and anterior chamber depth are parameters that imply the morphology of the eye. In the present study, both the AL and ACD were associated with height, even though SE, the standard index of myopia, not associated with it. Although AL and ACD do not represent the refractive status directly, these parameters should be taken into consideration when investigating refractive error.

The heritability of refractive error and ocular biometrics in this study was higher than those reported previously in other studies in Asia. In a Taiwanese population, two studies reported the heritability of refractive error; Tsai et al.[33] estimated the heritability of SE and AL as 0.33 and 0.67, respectively, from 41 MZ twins, 17 DZ twins and 13 siblings, and Yeh et al.[44] reported the heritability of SE as 0.56 with 33 MZ twins and 10 DZ twins. However, the Guangzhou Twin Eye Study investigated the heritability of refractive error with a sufficient sample size including 357 MZ twins and 206 DZ twins and reported that the heritability of AL and ACD was 0.88 and 0.89, which were higher than the estimated heritability in the Taiwanese population.[45] Therefore, the smaller heritability estimates from the studies in the Taiwanese population might be due to small sample sizes. Further research is required to understand the genetic effect on myopia in Asian populations.

The estimated narrow sense heritability in this study was comparable or lower than those found in western countries. A Danish study reported that the heritability of SE, AL and ACD was estimated to be 91%, 94% and 94%, respectively, from 53 MZ twins and 61 DZ twins.[36] The Gene in Myopia (GEM) study in Australia showed that the heritability of SE, AL and ACD was 75% and 88%, 92% and 94%, 78% and 51% in males and females, respectively, using 345 MZ twins and 267 DZ twins.[35] In UK, the Twin Eye Study found that the heritability of SE and CA was 86% and 18%, respectively.[34] Given the results of the previous classical twin studies, the present study showed more conservative heritability estimates in general. However, the previous studies could have the potential bias of inflating heritability caused by an assumption in classical twin studies that MZ twins and DZ twins share the same environment.[46] The present study could avoid the possibility of overestimating the heritability by using the extended family and the variance component methods.

There are several limitations in this study. First, even though the surrogate of near work has been suggested to be education, income and occupation, there might be more accurate markers to evaluate the effect of near work on myopia. Additionally, due to the lack of data, this study could not examine the effect of occupation on myopia. Second, the fact that the MZ twins exceeded the DZ twins by nearly 5 times could lead to some bias. This was due to the exclusion of opposite-sex twins by design in the Healthy Twin Study cohort. The largely different sample size between the MZ twins and DZ twins could lead to selection bias. However, selection bias occurs when the direction of effect is differential between the MZs and DZs. Therefore, it is unlikely that the differential participation between MZs and DZs would influence the findings of the study.

V. CONCLUSION

In conclusion, this study confirmed that education as a surrogate of near work had a substantial impact on the risk of myopia, and the genetic influence of refractive error was strong in a Korean population. With high heritability of myopia, the recent increase in the prevalence of myopia, especially in East Asia, could be because the growing educational concern causes the myopia gene to trigger a high penetrance. Further studies are required to identify genetic factors and examine gene-environment interactions, and then, personalized prevention and treatment should be implemented in the future.

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VII. Abstract in Korean（국문초록）

한국인의 근시와 관련된 유전 및 환경요인 분석

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배경: 최근 아시아 지역에서 근시 유병률이 급격히 증가하면서, 근시에 대한 보건학적 중요성이 대두되고 있다.

목적: 근시에 대한 유전 및 환경적 영향을 한국 가족-쌍둥이 코호트를 통해 알아보고자 한다.

방법: 한국 가족-쌍둥이 코호트에서 안과검사를 받은 1,508명 (일란성 쌍둥이 240쌍, 이란성 쌍둥이 45쌍, 일반 가족구성원 938명)이 분석에 포함되었다. 구면렌즈대응치, 안축장 길이, 전방깊이, 각막난시는 자동굴절검사, 각막곡률반경검사, 각막지형도검사, 초음파 검사를 통해 측정되었다. 교육수준과 소득수준이 굴절오류에 미치는 영향을 파악하기 위하여, 혼합 모형을 사용한 다중선형회귀분석을 수행하였으며, 구면렌즈 대응치 -0.75 디옵터 이하를 근시군으로 설정하여, 교육수준 및 소득수준과 근시에 한 연관성을 다중로지스틱회귀분석을 시행하여 파악하였다. 유전적 영향을 파악하기 위하여, 가족관계 내부 상관분석을 계산하고, 유전율을 추정하였다.

결과: 교육수준이 높을수록, 낮은 구면렌즈대응치, 긴 전방깊이와 관련이

있었으며, 소득수준이 높을수록, 낮은 구면렌즈대응치, 긴 안축장 길이, 긴 전방깊이와 관련이 있었다. 교육수준은 근시와 유의한 연관성을 보였다 (OR=1.84, 95% CI: 1.12-3.01). 가족관계 내부 상관분석은 모든 안구생체계측치에 대해서, 일란성 쌍둥이가 다른 가족 구성원의 경우보다 높게 나타났다. 유전율은 구면렌즈 대응치, 안축장 길이, 전방 깊이 및 각막난시에 대해서 각각, 0.67 (0.59-0.76), 0.78 (0.69-0.87), 0.77 (0.69-0.84), 0.18 (0.02-0.34)으로 나타났다.

결론: 교육수준과 소득수준은 굴절오류에 유의한 영향을 미치며, 교육수준은 근시와 유의한 연관성이 있음이 확인되었다. 또한, 한국인에서 근시 및 안구생체계측치에 미치는 유전적 영향이 상당한 것으로 나타났다. 최근의 급격한 근시 유병률의 증가는, 높은 유전율을 고려해보건대, 유전과 환경간의 상호관계에 의한 결과임을 유추해볼 수 있다. 따라서, 근시와 관련된 유전 요인의 규명과 유전과 환경간의 상호관계를 확인하는 후속연구들이 필요할 것으로 보인다.

주요어: 근시, 굴절오류, 유전율, 한국 가족-쌍둥이 코호트

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